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Review

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Brain evolution and development: adaptation, allometry and constraint

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Phenotypic traits are products of two processes: evolution and development. But how do these processes combine to produce integrated phenotypes? Comparative studies identify consistent patterns of covariation, or allometries, between brain and body size, and between brain components, indicating the presence of significant constraints limiting independent evolution of separate parts. These constraints are poorly understood, but in principle could be either developmental or functional. The developmental constraints hypothesis suggests that individual components (brain and body size, or individual brain components) tend to evolve together because natural selection operates on relatively simple developmental mechanisms that affect the growth of all parts in a concerted manner. The functional constraints hypothesis suggests that correlated change reflects the action of selection on distributed functional systems connecting the different sub-components, predicting more complex patterns of mosaic change at the level of the functional systems and more complex genetic and developmental mechanisms. These hypotheses are not mutually exclusive but make different predictions. We review recent genetic and neurodevelopmental evidence, concluding that functional rather than developmental constraints are the main cause of the observed patterns.

1. How brains evolve: the importance of scaling relationships

The components of any adaptive complex by definition undergo coordinated evolution. Brains, bodies and individual brain components therefore exhibit distinctive patterns of correlated evolution. But what do these patterns tell us about the roles of adaptation and constraint in shaping phenotypes? In particular, how and to what extent do constraints imposed by shared developmental programmes dictate allometric relationships between components, limiting their response to selection? These questions have shaped two key debates central to how we view brain evolution: the functional relevance of brain size and the adaptive potential of brain structure [1–3]. These debates hinge on whether observed patterns of scaling relationships, between brain and body size or different brain components, are the product of selection to maintain functional correspondence or constraints imposed by shared developmental programmes. Crucially, however, a sound understanding of the significance of scaling relationships in brain evolution has been limited by a lack of data on the genetic and developmental mechanisms that regulate brain size and structure. Here we discuss how recent discoveries about the genetic control of neural development shed new light on the issue.

(a) Brain: body coevolution and the importance of size

One early conclusion of comparative neuroanatomy was the simple observation that animals with larger bodies have larger brains [4]. Deviation from this pattern may reveal levels of 'cephalization', or 'progressive' brain expansion, reflecting cognitive ability [4]. This led to models of brain evolution that emphasize 'passive growth', caused by an indirect response to selection on body size, and 'active growth' that increases brain size relative to body size [5]. However,

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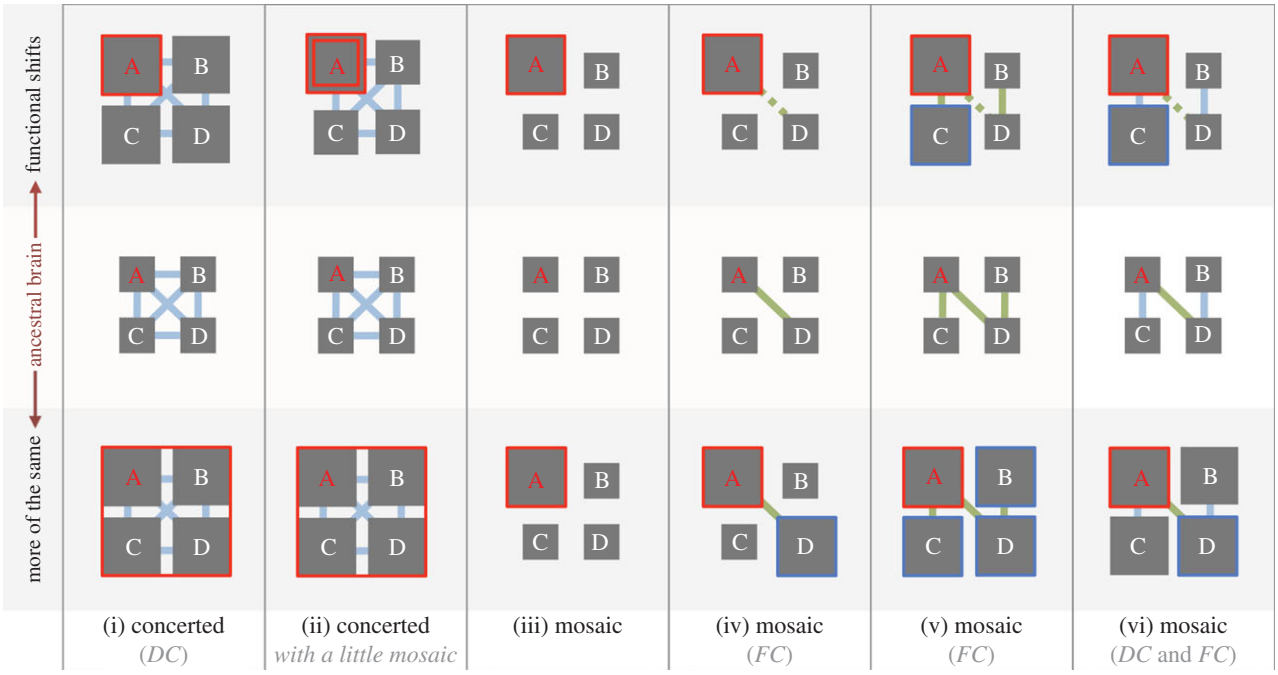

Figure 1. Origins of evolutionary constraints and covariance. Six scenarios that show how selection on one brain component (A) may cause coordinated changes throughout the system. The ancestral system is shown in the middle row; blue connections indicate developmental constraints (DC) and green connections indicate functional constraints (FC). Red outlines indicate the component(s) under primary selection; blue outlines indicate component(s) under secondary selection following changes in A. (i) Concerted brain evolution driven by DC: selection on A results in concerted expansion of all brain components. (ii) Concerted evolution with a small contribution of mosaicism: the evolution of new functions may be associated with an overall expansion of the system with a 'top up' for A driven by independent developmental mechanisms (top row). (iii) Mosaic evolution: a complete lack of constraint allows A to evolve independently. (iv) Mosaic evolution with FC: functional dependence between A and D means selection for A creates secondary selection for D to maintain the relationship between A and D (bottom row). If this functional relationship changes, A may be able to evolve without co-incident shifts in D (top row). (v) Mosaic evolution with system-wide functional dependence: selection on A will create secondary selection on the entire system (bottom row), patterns of covariance would appear identical to i and ii. If the functional connection changes between A and D, sub-networks A–C may evolve without co-incident shifts in A–D (top row). (vi) Mosaic evolution with partial DC and FC: If sub-networks A–C and B–D are developmentally linked internally, but functionally linked to other sub-networks, selection on A will result in a combination of secondary selection on D to maintain their functional relationship (lower row) and concerted expansion (of C and B) due to DC; the result is identical to i, ii and v. If the functional relationship changes between A and D, A may be able to respond without co-incident shifts in B–D but will still be accompanied by a 'neutral' change in C.

there is minimal evidence as to how the joint developmental control of brain and body size could be achieved. Brain and body development have notably different ontogenetic trajectories; for example, in mammals brain growth ceases long before body growth, and prenatal brain growth, during which the majority of neurogenesis occurs, is evolutionarily and genetically dissociable from postnatal brain growth [6–9]. In other vertebrates where the brain grows continuously through adulthood, brain and body growth trajectories may still vary. For example, brain growth in Crocodilia is continuous but slows with age, relative to body growth [10]. Any developmental mechanism that coordinates brain and body size must therefore act at multiple developmental stages, and in multiple tissues. While several hypotheses have been suggested, from developmental programming that fixes the number of cycles a neural progenitor cell undergoes [11] to growth-hormone mediated control of body growth via hypothalamus/pituitary secretions [12,13], they currently lack empirical support, while interspecific transplantation experiments in birds [14] suggest that body size does not control brain growth. This implies brain development is determined independently of somatic growth.

(b) Specialization of brain structure and development

Brains consist of individual components grouped within functionally differentiated neural systems. The extent to which these components can evolve independently of overall brain size has been keenly debated. At the extremes of this debate are the 'concerted' (figure 1, scenario (i)) and 'mosaic' (figure 1, scenario (iii)) models of brain evolution. The key conceptual difference between these hypotheses is the interpretation of the *cause* of allometric scaling among brain components.

The mosaic brain hypothesis [15] argues that variation in the size of individual brain components reflects adaptive divergence in brain function mediated by selection [16–19]. Barton & Harvey [15] demonstrated that patterns of covariance among mammalian brain components closely correspond to their anatomical and functional connectivity, suggesting that functional, rather than developmental, constraints drive allometric scaling between brain components. On this view, major brain components evolve together because functional systems cut across and connect them. Notably, this pattern of functional coevolution pervades biological levels, being apparent among component volumes [15,20] as well as at the levels of sub-component volumes [21,22] and cellular composition [23].

This evolutionary model of brain structure driven by region, or network-specific selection, is challenged by the concerted brain hypothesis, which instead argues that brains evolve predominantly by global alterations to the duration of neurogenesis, increasing or decreasing all components together [24,25]. This model explains allometries between brain components as the product of a highly conserved order of neurogenesis, with structures completing neurogenesis late

in development (such as the neocortex) growing disproportionately large with evolutionary increases in brain size. This hypothesis has important implications as it suggests a reduced or simpler role for selection in shaping brain structure, emphasizing the role of constraints on brain structure based on developmental conservatism. The mosaic hypothesis does not rule out such developmental integration, but suggests that where it is present it will be the product of selection to maintain functional correspondences [15].

These models are not mutually exclusive, but their relative contributions to variation in brain structure are debated. Discriminating between alternative sources of evolutionary constraint using only comparative volumetric data is challenging as similar patterns of covariation among major brain components could be produced by alternative mechanisms (figure 1). The two hypotheses can, however, be discriminated at the level of functional systems. A common misconception of the mosaic hypothesis is that it explains only a small proportion of variation (i.e. the residual variation that persists after accounting for overall brain size [25]). However, the hypothesis is not that mosaic evolution shapes residual volumes of individual components *per se*, but that it shapes functional systems as a whole. Selection on such systems cause functionally connected components to evolve in a coordinated manner such that patterns of covariation reflect functional, rather than developmental constraints (DC; figure 1, scenarios (iv), (v)). The mosaic hypothesis also explains features of brain evolution that are not predicted under a model emphasizing conserved developmental programmes, including (i) the presence of partial correlations among individual components that correspond to functional connections and which are similar, but not identical, in different phylogenetic groups [15,20,21]; (ii) evidence that individual components of neural systems can deviate from general patterns of correlated evolution [15,21]; and (iii) interspecific variation in component size that is more strongly correlated with ecology than with overall brain size. These observations suggest patterns of covariance between components can themselves evolve in response to changes in selection pressure.

2. Discriminating selection from constraint: new approaches to open questions

These evolutionary models of brain size and structure make contrasting predictions about the causes and consequences of scaling relationships that can be tested by studying the cellular basis of volumetric variation and dissecting the genetic basis of phenotypic variation. The concerted model suggests the majority of variance in a component size will be explained by a genetic correlation with total brain size, while the mosaic model predicts more independent genetic bases for different traits. Revealing the proximate bases of brain evolution therefore has the potential to resolve questions regarding the capacity for selection to act on the brain:

— Is coevolution due to selective covariance, resulting from selection acting independently on multiple traits, or pleiotropy?
— Can selection act on loci with specific effects on individual components?
— How frequently, when and why does selection act on loci with global effects relative to loci with local effects?
— Does selective covariance drive the evolution of integrated development?

Here, focusing on vertebrate brain evolution, we identify converging insights from multiple fields to discuss the causes and consequences of tissue scaling in brain evolution.

(a) Selective decoupling of coevolving traits

Interspecific variation provides straightforward evidence that brain components can vary in size independently of one another. This literature is reviewed and critiqued elsewhere [15,20,22,26], here we instead focus on new data from comparisons *within* species, and what these reveal about genetic correlations between brain traits. Artificial selection studies provided the initial empirical evidence for genetic covariance between brain and body size by demonstrating a concurrent response in brain size when selecting for body size [27–29]. However, additional experiments have demonstrated that artificial selection can alter relative brain size through specific changes in brain volume [30]. These results are supported by data from domesticated animals, themselves the products of long-term artificial selection. Compared to their wild ancestors, several domesticated species show major grade-shift in allometric scaling between brain and body mass, caused by a specific reduction in brain mass [31]. This capacity for a decoupling of brain and body size evolution is further bolstered by comparative studies that show these traits can evolve with distinct evolutionary patterns over long time periods [8,32–35]. Importantly, some of these cases indicate specific selection on brain mass, not body mass [8,35].

Similarly, selection experiments for specific motor behaviours have had a targeted effect on midbrain volume, independently of other brain regions [36]. Domesticated brains also show divergence in brain structure, with differential contraction and sometimes expansion of individual brain components [31]. The expansion of the hippocampus in homing pigeons (*Columbia livia*) [37] and selective decrease in the size of the lateral geniculate nucleus of domestic cats compared with Spanish wildcats [38] provide notable examples.

Until relatively recently, there were few examples of how wild populations respond to contrasting selection pressures on brain morphology on a micro-evolutionary time scale [39]. This has begun to change, with several studies examining evidence of local adaptation between recently diverged populations. These have identified mosaic patterns of brain evolution at a micro-evolutionary scale. Interpopulation differences in brain architecture, associated with environmental or behavioural variation, have been reported to affect telencephalon, optic tectum and cerebellum size in nine-spine sticklebacks (*Pungitius pungitius*) [40], telencephalon morphology in three-spine sticklebacks (*Gasterosteus aculeatus*) [41] and cerebellum size in migratory brown trout (*Salmo trutta*) [42], independently of overall brain size. These suggest conclusions derived from the products of artificial selection are not aberrant but may accurately reflect the evolvability of brain structure.

(b) Genetic architecture of brain structure within species

Quantitative genetics provides a direct approach to assess the genetic architecture underpinning variation in brain size and structure within species. It can identify how many genomic regions control phenotypic variation, and whether phenotypic covariation in distinct traits reflects underlying genetic

correlations (i.e. a common genetic basis) that imply the presence of pleiotropic effects, where variation in one gene affects multiple traits.

Selection experiments in rodents that reported a significant response in body mass when selection acted on brain mass [27–29] were influential in interpreting patterns of brain : body allometry despite the fact that the reported genetic correlations are not high enough to reflect strong constraints [43]. Indeed, in some strains there is no significant covariance between brain and body size [44], and the rank-order correlation between brain and body mass across strains is not significant [45]. These results imply some degree of genetic independence. This conclusion is supported by genome-wide mapping of quantitative trait loci that shows that there is little or no genetic covariance between brain and body size, or between sub-components of the brain [46]. Overall volume and neuron number of individual sub-components may also have independent genetic bases [47,48], implying that developmental models tying one to the other will have limited predictive power. Evidence for genetic independence between brain components has also been reported in sticklebacks and between chicken breeds [49,50]. In sticklebacks, genetic correlations between brain components are significantly less than unity, despite a relatively high correlation between brain and body size [49]. Hence, even where body size does constrain the evolution of brain size, brain structure may still undergo adaptive reorganization.

Phenotypic variation in populations or colonies of free-ranging primates mirror this pattern of genetic independence between brain traits. Structural traits in the brains of multiple primate species show evidence of independence both at the level of whole brain component volume and in different traits of a single component [51–53]. Where they exist, patterns of genetic covariance may even suggest counterintuitive patterns of covariance. For example, Rogers *et al*. [53] report a *negative* genetic correlation between cerebral volume and gyrification in both *Papio* and humans despite their *positive* evolutionary relationship during primate brain evolution [54] (but see [55]). Anatomical covariation [56] and genome-wide association studies in humans provide further evidence of independence in brain component variability [57,58]. Quantitative genetic analysis of brain size and structure in different species are therefore largely in agreement: although much is still to learn about the genetic architecture of brain structure, the hypothesis that widespread genetic constraints restrict patterns of independent variation is not currently supported.

(c) Molecular divergence and brain structure across species

Increased availability of molecular data has led to the identification of loci that contribute to species differences in brain size or structure. The functional effects of these genes provide an initial assessment of whether selection acts on local or global phenotypes in the brain across longer evolutionary periods. Some of these loci appear to affect brain size independently of body size. For example, two genes associated with human microcephaly, *ASPM* and *CDK5RAP2*, show signatures of co-evolution with brain mass, but not body mass [9,59]. Sequence variation in several microcephaly genes has also been associated with variation in human brain volume [60,61]. *ASPM* and *CDK5RAP2* regulate proliferative divisions of neural progenitor cells during early brain development [62]. This, and the relatively conserved brain architecture of individuals with microcephaly [63] and *ASPM* knock-out mice [64], may suggest they act to delay the time schedule of neurogenesis [39]. Selection on genetic variation with this effect could conceivably cause a concerted pattern of brain evolution. A similar developmental change may underpin the response to artificial selection on brain size in guppies (*Poecilia reticulata*) [30], which is associated with the changes in the expression level of *Ang-1* [65]. *Ang-1* regulates the neurogenic output of neural progenitor cells [66] and its increased expression may promote a general expansion in brain size.

Elsewhere, however, there is evidence that selection has shaped the evolution of genes with more specific, localized developmental effects. *Nin*, for example, is implicated in the prolonged neurogenic output of cortical neural progenitors [67] and evolved adaptively in primates in association with variation in the number of neurons per unit area of cortex [68]. Several further loci with human-specific accelerated rates of evolution [69,70], loss of function [71] or duplication [72] are implicated in evolutionary changes specific to the developing forebrain. For example, the rapid evolution of an enhancer, *HARE5*, drives upregulation of *FZD8* expression specific to the lateral telencephalon, resulting in a greater neurogenic output during corticogenesis [70]. Another enhancer, *HAR142*, with a human-specific acceleration in substitution rate alters the expression of *NPAS3*, a transcription factor implicated in forebrain development [69]. Human-specific loss of a conserved regulatory region near *GADD45G*, drives region-specific expression and cell-cycle dynamics in the sub-ventricular zone of the preoptic area, thalamus and hypothalamus [71]. Finally, a Rho GTPase activating gene, *ARHGAP11B*, the product of a duplication event on the terminal human lineage, promotes self-renewal of radial glial cells during cortical neurogenesis [72].

A further suite of loci with human-specific patterns of molecular evolution appear to alter the regulation of neurite outgrowth and wiring [73,74], key processes influencing brain component volumes. The developmental effects of interspecific variation in these genes appear to act on specific areas of the developing brain. The most well-studied example of this is the role of *FOXP2* in speech development and evolution [73]. Human *FOXP2* has two derived amino acid substitutions that specifically alter dopamine concentrations, dendrite length and synaptic plasticity in the basal ganglia of a transgenic mouse model [73], and purkinje cell function in the cerebellum [75]. Differential expression of another FOX family gene, *FOXP1*, in the avian telencephalon also provides support for the region-specific action of key transcription factors in moderating mosaic patterns of brain evolution [76]. The human-specific duplication of *SRGAP2* provides a further example of localized effects, in which antagonistic interactions between the duplicated copies result in altered expression profiles that affect dendritic morphology during neocortical maturation [74,77]. Together, these results underline the capacity for selection to act on genetic variants that effect distinct neurodevelopmental processes to modify fine details of brain structure, supporting mosaic evolution within and between brain components.

(d) Volumetric data may disguise hidden diversity: insights from cellular scaling

The concerted model of brain evolution specifies that late-developing structures (notably the neocortex) grow disproportionately large during episodes of brain expansion

[24,25,78]. This is argued to occur as a result of increased rounds of neurogenesis produced by an overall extension of the period of development. Since the volume allometries among brain structures are postulated to be driven by differing production of neurons, the concerted model predicts that the proportion of total brain volume a component occupies should be closely related to the proportion of total neuron number in that structure. For example, the neocortex should not only be disproportionately large in large-brained species, but also contain a disproportionately large number of neurons. Recent data in fact suggest volumetric and neuron number proportions are uncorrelated; the ratio between neuron numbers in neocortex and cerebellum is relatively constant, despite substantial interspecific variation in the ratio of their volumes [79–81]. Within the neocortex, frontal regions become disproportionately large as overall brain size increases, but this is not matched by a disproportionate increase in neuron number, because neuron density declines more steeply in frontal than in posterior cortex [81,82]. This suggests that volumetric allometries reflect a trade-off between volume and neuron densities, with steeper declines in frontal neuron density with increasing overall size compensated by steeper increases in volume.

This pattern is not predicted by the 'late equals large' hypothesis associated with the concerted model of brain evolution [24,25]. Under this hypothesis, late-maturing structures grow relatively larger in large brains because they acquire relatively more neurons due to increased duration of neurogenesis (see fig. 4 in [25]). Charvet *et al.* [83] suggest that the rostrocaudal gradient in cortical neuron density, and the fact that this gradient is steeper in large-brained species, matches the predictions of the 'late equals large hypothesis', as late-maturing caudal cortex has higher neuron densities. Yet the volumetric allometry is opposite to the pattern predicted; as brain size increases the caudal cortex becomes smaller as a proportion of cortical size, while the rostral cortex becomes larger. Furthermore, a striking feature of these data is the substantially higher number of cortical neurons in primate brains than in rodent brains of similar size [79], a pattern consistent with mosaic increase in cortical size in primates [15] and not with a general allometric rule relating cortical neuron numbers to brain size [24,25], or the claim that the number of neurons in a structure 'is very highly predictable in allometric scaling of whole brain size' [84].

Further data on the cellular composition and neuron density of mammalian brains demonstrate clade-specific shifts in the relationship between volume and neuron number [79], consistent with evidence these traits have distinct genetic bases [47,48]. The apparent similarity in volumetric scaling relationships of different brain structures across mammals [24], which is itself challenged [85], does not reflect uniformity in neuron number [80,83]. This runs counter to the hypothesis that developmental programmes of neurogenesis are widely conserved [25,86]. Instead, it demonstrates that meaningful variation in the timing or rate of brain development exists and facilitates region-specific alterations in the development of neuron number [85,87].

(e) Developmental models of mosaic evolution

If the size of brain components can evolve independently, how do these mosaic changes occur and how is size regulated at a local level? Recent data suggest three potentially non-mutually exclusive ways mosaic evolution can be achieved (figure 2): (i) shifts in fate-determining signals, (ii) region-specific delays in the schedule of neurogenesis and (iii) variation in cell-cycle rates.

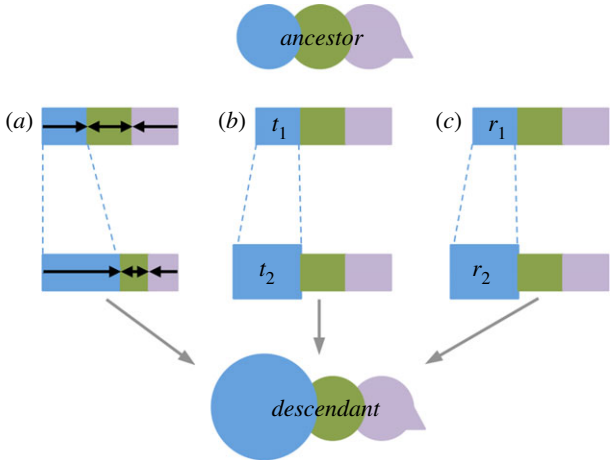

Figure 2. Developmental routes to mosaic brain evolution. Selection can modify the relative size of individual brain components through three routes, as follows. (*a*) Modifying how the progenitor pool of cells that produce neurons is divided between regions by changing the boundaries of expression gradients of morphogens. A role for developmental patterning in creating variation in brain structure between species has been demonstrated in derived, cave dwelling populations of *Atyanax mexicanus* [88] and ecologically divergent cichlids in Lake Malawi [89]. (*b*) Prolonging the period of cell division in the progenitor pool of cells destined to form a specific component. Expansion of specific brain components has been linked to interspecific variation in region-specific duration of neurogenesis in Passerimorphae [90–92], nocturnal *Aotus* monkeys [93] and Mammalia more generally [94]. (*c*) Accelerating the rate at which cells divide within a conserved developmental schedule. Variation in cell-cycle rate prior to the onset of neurogenesis is thought to contribute to interspecific differences in the relative size of the telencephalon in galliform birds [95].

Shifts in the boundaries of expression profiles of fate-determining signals can alter what proportions of neural progenitors are assigned to each brain region. This effect has been demonstrated between closely related but ecologically divergent species of *Astyanax* cavefish and African cichlids [88,89], and may contribute to other examples of mosaic brain evolution [90,95]. In *Astyanax*, changes in the expression domains of a secreted morphogen, *Shh*, produce region-specific changes in multiple brain regions, in particular, hypothalamus size [88]. In African cichlids, species differences in morphogen patterning along the anterior–posterior brain axis cause specific, differential expansion of the telencephalon [89].

Interspecific variation in the schedule and timing of neurogenesis provides an alternative route to region-specific expansion. Telencephalon expansion in Passerimorphae (parrots and passerine birds) is caused by a specific delay in telencephalic neurogenesis [90–92] that drives an increase in the number of progenitor cells destined for the telencephalon. This delay is accompanied by the emergence of a 'sub-ventricular zone' [92], analogous to that observed in large-brained mammals which is thought to underpin cortical expansion [94]. A similar mechanism may facilitate the expansion of the retina in nocturnal owl monkeys (*Aotus azarae*) [93].

Despite an ever-increasing understanding of the mechanisms of cell division, how cell proliferation is controlled to produce the correct number of neurons remains an

ill-answered question, but one central to understanding how tissue size is regulated and constrained. For example, mechanisms of local control of proliferation may be necessary to produce mosaic patterns of evolution. Recently, Buzi *et al*. [96] demonstrated the potential for descendent cells to regulate the duration of proliferative division in their own progenitor pools through 'integral feedback' mediated by secreted molecules. Under this model, the strength of an inhibitive signal on cell division increases as descendent cells accumulate until it causes a cessation of proliferation. Notably, this is only a stable size-determining system in cell lineages with intermediate cells and lineage branching, as is the case in neurogenesis [97]. In other tissues, members of the TGF-β gene family, which have known roles in cell differentiation [98] and brain development [99], function as the signal molecule. TGF-β signals are only effective across small spatial scales suggesting local feedback operates at a tissue-specific rather than whole organ level [96]. It is an intriguing hypothesis that modification of such signals would allow local control and variation in cell proliferation, facilitating mosaic evolution.

Accelerating the cell-cycle rate within a conserved time schedule provides an alternative route to region-specific changes in neuron number [100]. In galliform birds, a short period of accelerated cell cycling before the onset of neurogenesis explains much of the variance in brain size between chickens and bobwhite quail [91,101]. The cell cycle of cortical precursors is longer in primates than in rodents, which also differ in the relative size of proliferative and post-mitotic compartments, and the presence of sub-populations of cell types. [102]. This provides a potential developmental mechanism for the relative expansion of the primate cortex, indeed, fixed differences in several genes linked to human brain expansion accelerate cell cycle rates [70,71].

Although aspects of the schedule of neurogenesis may be partly conserved [24,25,103], this does not appear to represent a consistent prohibitive constraint to region-specific divergence, when favoured by selection. Variation in the timing of neurogenesis, cell-cycle rates and patterning of progenitor pools suggest these processes can, at least in part, evolve independently [104], offering alternative routes through which selection can act. These three routes to the diversification of brain structure may take effect at different stages of development. For example, a purely concerted model of brain evolution posits variation along a conserved developmental schedule. This would predict that the growth curves of different brain regions are similar across species with contrasting total brain sizes. By contrast, variation in the gene expression patterns that determine brain modularity may effect early development, meaning the relative expansion or contraction of brain components should be observed once boundaries between structures are established causing a grade-shift in the growth curve of brain components [105]. Volumetric variation caused by region-specific changes in the duration or cell-cycle rate of neurogenesis may instead only become manifest later in development, with an initially conserved architecture giving way to greater interspecific variation as development progresses, associated with variation in the slope of the growth curve.

Comparative analysis of component growth may provide a quantitative approach to assess the frequency of different developmental mechanisms once sufficient data are available. Existing models that take such an approach are, unfortunately, derived from a relatively small ($n = 18$) and incomplete dataset of developmental events in mammals [24,25,103]. Despite supporting a largely concerted view of brain evolution [24,25,103], the model also reveals notable examples of taxon-specific heterochrony, and correlations between developmental events across species are often only moderate or even non-significant (see associated commentary on [25]), implying the capacity for selection to produce interspecific variation at multiple developmental time points.

3. Future directions: the genetic toolbox for comparative neuroanatomy

In recent years, new data from disparate fields of experimental evolution, comparative biology, quantitative and molecular genetics, and development together demonstrate the presence of independent variation in separate components of brain systems, and the ability of selection to act upon it. The emergence of new techniques in these fields should continue to accelerate our understanding of the causes of tissue scaling. Large, high-quality phenotypic datasets [79,106], comparative methods to detect selection on phenotypes [107], and new sequencing methods that increase the power of quantitative genetics and phylogenetic tests of gene–phenotype associations will allow us to examine how patterns of genetic correlations observed within species persist at a macroevolutionary scale to test hypotheses about how brains evolve. When combined, these advances will provide novel insights into the influence of functional and developmental constraints on brain evolution. For example:

1. How does selection negotiate or re-shape genetic correlations between components? By coupling quantitative genetics with selection experiments favouring expansion of total brain size, an individual component or a pair of components, the genetic architecture before and after a selection event could be assessed. This would permit an examination of whether genetic correlations channel and constrain brain evolution, or whether selection can re-shape or produce genetic integration between brain components. For example, if the response of multiple components is due to a common developmental shift variation in the size of these structures should show significant genetic correlations (e.g. figure 1, scenario (i)), if they do not this may suggest secondary selection on independent loci to maintain functional associations (e.g. figure 1, scenario (v)).
2. What explains the presence of genetic correlations? Where present, the strength of genetic correlations between components could be combined with data on developmental (or evolutionary) origin and connectivity, to test whether genetic correlations evolve in response to functional integration (figure 1, scenario (v)), or reflect patterns of conserved developmental origin (figure 1, scenario (i)).
3. Do genes targeted by selection have local (figure 1, scenario (iii)) or global (figure 1, scenario (i)) developmental effects? The continued pursuit of genes regulating species differences in brain size and structure will provide a direct assessment of whether the evolution of separate brain components can be shaped by selection independently of total brain size through functional assays of the effects of variation in candidate gene sequence or regulation.
4. Does selective expansion of peripheral sensory structures cause a concerted expansion of connected central structures

as a result of activity-dependent development? By identifying genes with specific effects on neural development of peripheral structures, functional analyses could examine how increased input to connected structures alter their development. These functional associations could drive the concerted evolution of connected brain regions if projection neurons or morphogens originating from peripheral structures influence patterns of growth in related brain components (scenario (vi) in figure 1).

5. Do differences in the relationship between volume and neuron number across brain structures, and across mammalian clades, reflect differences in the duration or rate of cell division among neural progenitors? Comparative development of species representing alternative scaling relationships can be used to test models of mosaic evolution.
6. Did the human brain evolve by an extension or exaggeration of conserved genetic and developmental processes that shape variation in brain size and structure across primates? And to what extent is human brain expansion the product of unique neurodevelopmental changes? Functional analysis of the developmental and physiological effect of genes targeted by selection during independent episodes of brain expansion may reveal functional variation in adaptive neural traits.

A greater understanding of the causes of covariance and coevolution between brain components will in turn further our understanding of how brains adapt to changing selection pressures. The relative importance of concerted and mosaic brain evolution may vary across time and taxa, dependent on the selection pressures acting on brain size and structure. Understanding the circumstances under which selection favours alternative route of phenotypic evolution is a significant challenge, but will be central to understanding how brains evolve.

Competing interests. We declare we have no competing interests.

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References

1. White J, Gould S. 1965 Interpretation of the coefficient in the allometric equation. *Am. Nat.* **99**, 5–18. (doi:10.1086/282344)
2. Gould SJ. 1966 Allometry and size in ontogeny and phylogeny. *Biol. Rev. Camb. Philos. Soc.* **41**, 587–640. (doi:10.1111/j.1469-185X.1966.tb01624.x)
3. Jerison H. 1973 *Evolution of the brain and intelligence*. New York, NY: Academic Press.
4. Dubois E. 1897 Sur le rapport de l' encephale avec la grandeur du corps chez les Mammiferes. *Bull. Soc. Anthr. Paris* **4**, 337–374. (doi:10.3406/bmsap.1897.5705)
5. Aboitiz F. 1996 Does bigger mean better? Evolutionary determinants of brain size and structure. *Brain Behav. Evol.* **47**, 225–245. (doi:10.1159/000113243)
6. Atchley WR. 1987 Developmental quantitative genetics and the evolution of ontogenies. *Evolution* **41**, 316–330. (doi:10.2307/2409141)
7. Barton RA, Capellini I. 2011 Maternal investment, life histories, and the costs of brain growth in mammals. *Proc. Natl Acad. Sci. USA* **108**, 6169–6174. (doi:10.1073/pnas.1019140108)
8. Montgomery SH, Capellini I, Barton RA, Mundy NI. 2010 Reconstructing the ups and downs of primate brain evolution: implications for adaptive hypotheses and *Homo floresiensis*. *BMC Biol.* **8**, 9. (doi:10.1186/1741-7007-8-9)
9. Montgomery SH, Capellini I, Venditti C, Barton RA, Mundy NI. 2011 Adaptive evolution of four microcephaly genes and the evolution of brain size in anthropoid primates. *Mol. Biol. Evol.* **28**, 625–638. (doi:10.1093/molbev/msq237)
10. Ngwenya A *et al.* 2013 The continuously growing central nervous system of the nile crocodile (*Crocodylus niloticus*). *Anat. Rec.* **296**, 1489–1500. (doi:10.1002/ar.22752)
11. Williams RW, Herrup K. 1988 The control of neuron number. *Annu. Rev. Neurosci.* **11**, 423–453. (doi:10.1146/annurev.ne.11.030188.002231)
12. Tannenbaum GS, Guyda HJ, Posner BI. 1983 Insulin-like growth factors: a role in growth hormone negative feedback and body weight regulation via brain. *Science* **220**, 77–79. (doi:10.1126/science.6338593)
13. Deacon TW. 1990 Problems of ontogeny and phylogeny in brain-size evolution. *Int. J. Primatol.* **11**, 237–282. (doi:10.1007/BF02192870)
14. Balaban E, Teillet M, Le Douarin N. 1988 Application of the quil-chick chimera system to the study of brain development and behaviour. *Science* **241**, 1339–1342. (doi:10.1126/science.3413496)
15. Barton RA, Harvey PH. 2000 Mosaic evolution of brain structure in mammals. *Nature* **405**, 1055–1058. (doi:10.1038/35016580)
16. Eisenberg J. 1981 *The mammalian radiations: an analysis of trends in evolution, adaptation, and behavior*. Chicago, IL: University of Chicago Press.
17. Stephan H, Frahm H, Baron G. 1981 New and revised data on volumes of brain structures in insectivores and primates. *Folia Primatol.* **35**, 1–29. (doi:10.1159/000155963)
18. Harvey PH, Krebs J. 1990 Comparing brains. *Science* **249**, 140–146. (doi:10.1126/science.2196673)
19. de Winter W, Oxnard CE. 2001 Evolutionary radiations and convergences in the structural organization of mammalian brains. *Nature* **409**, 710–714. (doi:10.1038/35055547)
20. Iwaniuk AN, Dean KM, Nelson JE. 2004 A mosaic pattern characterizes the evolution of the avian brain. *Proc. R. Soc. Lond. B* **271**, S148–S151. (doi:10.1098/rsbl.2003.0127)
21. Whiting BA, Barton RA. 2003 The evolution of the cortico-cerebellar complex in primates: anatomical connections predict patterns of correlated evolution. *J. Hum. Evol.* **44**, 3–10. (doi:10.1016/S0047-2484(02)00162-8)
22. Barton RA. 2007 Evolutionary specialization in mammalian cortical structure. *J. Evol. Biol.* **20**, 1504–1511. (doi:10.1111/j.1420-9101.2007.01330.x)
23. Lewitus E, Hof PR, Sherwood CC. 2012 Phylogenetic comparison of neuron and glia densities in the primary visual cortex and hippocampus of carnivores and primates. *Evolution* **66**, 2551–2563. (doi:10.1111/j.1558-5646.2012.01601.x)
24. Finlay B, Darlington R. 1995 Linked regularities in the development and evolution of mammalian brains. *Science* **268**, 1578–1584. (doi:10.1126/science.7777856)
25. Finlay BL, Darlington RB, Nicastro N. 2001 Developmental structure in brain evolution. *Behav. Brain Sci.* **24**, 263–278. (doi:10.1017/S0140525X01003958)
26. Healy SD, Rowe C. 2007 A critique of comparative studies of brain size. *Proc. R. Soc. B* **274**, 453–464. (doi:10.1098/rspb.2006.3748)
27. Fuller J, Geils H. 1972 Brain growth in mice selected for high and low brain weight. *Dev. Psychobiol.* **5**, 307–318. (doi:10.1002/dev.420050404)
28. Atchley WR. 1984 The effect of selection on brain and body size association in rats. *Genet. Res.* **43**, 289–298. (doi:10.1017/S0016672300026070)
29. Atchley WR, Riska B, Kohn LAP, Plummer AA. 1984 A quantitative genetic analysis of brain and body size associations. Their origin and ontogeny: data from mice. *Evolution* **38**, 1165–1179. (doi:10.2307/2408625)
30. Kotrschal A, Rogell B, Bundsen A, Svensson B, Zajitschek S, Brännström I, Immler S, Maklakov AA, Kolm N. 2013 Artificial selection on relative brain

size in the guppy reveals costs and benefits of evolving a larger brain. *Curr. Biol.* **23**, 168–171. (doi:10.1016/j.cub.2012.11.058)

31. Kruska DCT. 2005 On the evolutionary significance of encephalization in some eutherian mammals: effects of adaptive radiation, domestication, and feralization. *Brain Behav. Evol.* **65**, 73–108. (doi:10.1159/000082979)
32. Gonzalez-Voyer A, Winberg S, Kolm N. 2009 Distinct evolutionary patterns of brain and body size during adaptive radiation. *Evolution* **63**, 2266–2274. (doi:10.1111/j.1558-5646.2009.00705.x)
33. Montgomery SH, Geisler JH, McGowen MR, Fox C, Marino L, Gatesy J. 2013 The evolutionary history of cetacean brain and body size. *Evolution* **67**, 3339–3353. (doi:10.1111/evo.12197)
34. Fitzpatrick JL, Almbro M, Gonzalez-Voyer A, Hamada S, Pennington C, Scanlan J, Kolm N. 2012 Sexual selection uncouples the evolution of brain and body size in pinnipeds. *J. Evol. Biol.* **25**, 1321–1330. (doi:10.1111/j.1420-9101.2012.02520.x)
35. Finarelli JA, Flynn JJ. 2009 Brain-size evolution and sociality in Carnivora. *Proc. Natl. Acad. Sci. USA* **106**, 9345–9349. (doi:10.1073/pnas.0901780106)
36. Kolb EM, Rezende EL, Holness L, Radtke A, Lee SK, Obenaus A, Garland T. 2013 Mice selectively bred for high voluntary wheel running have larger midbrains: support for the mosaic model of brain evolution. *J. Exp. Biol.* **216**, 515–523. (doi:10.1242/jeb.076000)
37. Rehkämper G, Frahm HD, Cnotka J. 2008 Mosaic evolution and adaptive brain component alteration under domestication seen on the background of evolutionary theory. *Brain Behav. Evol.* **71**, 115–126. (doi:10.1159/000111458)
38. Williams RW, Cavada C, Reinoso-Suárez F. 1993 Rapid evolution of the visual system: a cellular assay of the retina and dorsal lateral geniculate nucleus of the Spanish wildcat and the domestic cat. *J. Neurosci.* **13**, 208–228.
39. Striedter GF. 2005 *Principles of brain evolution*. Sunderland, MA: Sinauer Associates.
40. Gonda A, Herczeg G, Merilä J. 2011 Population variation in brain size of nine-spined sticklebacks (*Pungitius pungitius*): local adaptation or environmentally induced variation? *BMC Evol. Biol.* **11**, 75. (doi:10.1186/1471-2148-11-75)
41. Park PJ, Bell MA. 2010 Variation of telencephalon morphology of the threespine stickleback (*Gasterosteus aculeatus*) in relation to inferred ecology. *J. Evol. Biol.* **23**, 1261–1277. (doi:10.1111/j.1420-9101.2010.01987.x)
42. Kolm N, Gonzalez-Voyer A, Brelin D, Winberg S. 2009 Evidence for small scale variation in the vertebrate brain: mating strategy and sex affect brain size and structure in wild brown trout (*Salmo trutta*). *J. Evol. Biol.* **22**, 2524–2531. (doi:10.1111/j.1420-9101.2009.01875.x)
43. Lande R. 1979 Quantitative genetic analysis of multivariate evolution applied to brain : body size allometry. *Evolution* **33**, 402–416. (doi:10.2307/2407630)
44. Belknap JK, Phillips TJ, O'Toole LA. 1992 Quantitative trait loci associated with brain weight in the BXD/Ty recombinant inbred mouse strains. *Brain Res. Bull.* **29**, 337–344. (doi:10.1016/0361-9230(92)90065-6)
45. Roderick TH, Wimer RE, Wimer CC, Schwartzkroin PA. 1973 Genetic and phenotypic variation in weight of brain and spinal cord between inbred strains of mice. *Brain Res.* **64**, 345–353. (doi:10.1016/0006-8993(73)90188-1)
46. Hager R, Lu L, Rosen GD, Williams RW. 2012 Genetic architecture supports mosaic brain evolution and independent brain–body size regulation. *Nat. Commun.* **3**, 1079. (doi:10.1038/ncomms2086)
47. Rosen GD, Williams RW. 2001 Complex trait analysis of the mouse striatum: independent QTLs modulate volume and neuron number. *BMC Neurosci.* **2**, 5. (doi:10.1186/1471-2202-2-5)
48. Airey DC, Lu L, Williams RW. 2001 Genetic control of the mouse cerebellum: identification of quantitative trait loci modulating size and architecture. *J. Neurosci.* **21**, 5099–5109.
49. Noreikiene K, Herczeg G, Gonda A, Balazs G, Husby A, Merilä J. 2015 Quantitative genetic analysis of brain size variation in sticklebacks: support for the mosaic model of brain evolution. *Proc. R. Soc. B* **282**, 20151008. (doi:10.1098/rspb.2015.1008)
50. Henriksen R, Andersson L, Jensen P, Wright D. In press. The domesticated brain: genetics of brain mass and brain structure in an avian species. *BioRxiv*, 066977.
51. Panizzon MS *et al.* 2009 Distinct genetic influences on cortical surface area and cortical thickness. *Cereb. Cortex.* **19**, 2728–2735. (doi:10.1093/cercor/bhp026)
52. Winkler AM, Kochunov P, Blangero J, Almasy L, Zilles K, Fox PT, Duggirala R, Glahn DC. 2010 Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *Neuroimage* **53**, 1135–1146. (doi:10.1016/j.neuroimage.2009.12.028)
53. Rogers J *et al.* 2010 On the genetic architecture of cortical folding and brain volume in primates. *Neuroimage* **53**, 1103–1108. (doi:10.1016/j.neuroimage.2010.02.020)
54. Zilles K, Armstrong E, Moser KH, Schliecher A, Stephan H. 1989 Gyrification in the cerebral cortex of primates. *Brain Behav. Evol.* **34**, 134–150.
55. Ventura-Antunes L, Mota B, Herculano-Houzel S. 2013 Different scaling of white matter volume, cortical connectivity, and gyrification across rodent and primate brains. *Front. Neuroanat.* **7**, 3. (doi:10.3389/fnana.2013.00003)
56. Gómez-Robles A, Hopkins WD, Sherwood CC. 2014 Modular structure facilitates mosaic evolution of the brain in chimpanzees and humans. *Nat. Commun.* **5**, 4469. (doi:10.1038/ncomms5469)
57. Toro R *et al.* 2013 Genomic architecture of human neuroanatomical diversity. *Mol. Psychiatry* **20**, 1011–1016. (doi:10.1038/mp.2014.99)
58. Hibar DP *et al.* 2015 Common genetic variants influence human subcortical brain structures. *Nature* **520**, 224–229. (doi:10.1038/nature14101)
59. Montgomery SH, Mundy NI. 2014 Microcephaly genes evolved adaptively throughout the evolution of eutherian mammals. *BMC Evol. Biol.* **14**, 120. (doi:10.1186/1471-2148-14-120)
60. Rimol LM *et al.* 2010 Sex-dependent association of common variants of microcephaly genes with brain structure. *Proc. Natl Acad. Sci. USA* **107**, 384–388. (doi:10.1073/pnas.0908454107)
61. Wang JK, Li Y, Su B. 2008 A common SNP of MCPH1 is associated with cranial volume variation in Chinese population. *Hum. Mol. Genet.* **17**, 1329–1335. (doi:10.1093/hmg/ddn021)
62. Thornton GK, Woods CG. 2009 Primary microcephaly: do all roads lead to Rome? *Trends Genet.* **25**, 501–510. (doi:10.1016/j.tig.2009.09.011)
63. Bond J *et al.* 2002 *ASPM* is a major determinant of cerebral cortical size. *Nat. Genet.* **32**, 316–320. (doi:10.1038/ng995)
64. Pulvers JN *et al.* 2010 Mutations in mouse *Aspm* (abnormal spindle-like microcephaly associated) cause not only microcephaly but also major defects in the germline. *Proc. Natl Acad. Sci. USA* **107**, 16 595–16 600. (doi:10.1073/pnas.1010494107)
65. Chen Y-C, Harrison PW, Kotrschal A, Kolm N, Mank JE, Panula P. 2015 Expression change in *Angiopoietin-1* underlies change in relative brain size in fish. *Proc. R. Soc. B* **282**, 20150872. (doi:10.1098/rspb.2015.0872)
66. Rosa AI, Gonçalves J, Cortes L, Bernardino L, Malva JO, Agasse F. 2010 The angiogenic factor *Angiopoietin-1* is a proneurogenic peptide on subventricular zone stem/progenitor cells. *J. Neurosci.* **30**, 4573–4584. (doi:10.1523/JNEUROSCI.5597-09.2010)
67. Wang X, Tsai J-W, Imai JH, Lian W-N, Vallee RB, Shi S-H. 2009 Asymmetric centrosome inheritance maintains neural progenitors in the neocortex. *Nature* **461**, 947–955. (doi:10.1038/nature08435)
68. Montgomery SH, Mundy NI. 2012 Positive selection on NIN, a gene involved in neurogenesis, and primate brain evolution. *Genes Brain Behav.* **11**, 903–910.
69. Kamm GB, López-Leal R, Lorenzo JR, Franchini LF. 2013 A fast-evolving human *NPAS3* enhancer gained reporter expression in the developing forebrain of transgenic mice. *Phil. Trans. R. Soc. B* **368**, 20130019. (doi:10.1098/rstb.2013.0019)
70. Boyd JL, Skove SL, Rouanet JP, Pilaz L-J, Bepler T, Gordân R, Wray GA, Silver DL. 2015 Human-chimpanzee differences in a *FZD8* enhancer alter cell-cycle dynamics in the developing neocortex. *Curr. Biol.* **25**, 772–779. (doi:10.1016/j.cub.2015.01.041)
71. McLean CY *et al.* 2011 Human-specific loss of regulatory DNA and the evolution of human-specific traits. *Nature* **471**, 216–219. (doi:10.1038/nature09774)
72. Florio M *et al.* 2015 Human-specific gene *ARHGAP11B* promotes basal progenitor amplification and neocortex expansion. *Science* **347**, 1465–1470. (doi:10.1126/science.aaa1975)
73. Enard W *et al.* 2009 A humanized version of *Foxp2* affects cortico-basal ganglia circuits in mice. *Cell* **137**, 961–971. (doi:10.1016/j.cell.2009.03.041)

74. Charrier C *et al.* 2012 Inhibition of SRGAP2 function by its human-specific paralogs induces neoteny during spine maturation. *Cell* **149**, 923–935. (doi:10.1016/j.cell.2012.03.034)
75. Fujita-jimbo E, Momoi T. 2014 Specific expression of *FOXP2* in cerebellum improves ultrasonic vocalization in heterozygous but not in homozygous *Foxp2* (R552H) knock-in pups. *Neurosci. Lett*. **566**, 162–166. (doi:10.1016/j.neulet.2014.02.062)
76. Garcia-Calero E, Martinez S. In press. FoxP1 protein shows differential layer expression in the parahippocampal domain among bird species. *Brain Behav. Evol*. **87**. (doi:10.1159/000446601)
77. Dennis MY *et al.* 2012 Evolution of human-specific neural *SRGAP2* genes by incomplete segmental duplication. *Cell* **149**, 912–922. (doi:10.1016/j.cell.2012.03.033)
78. Finlay BL, Clancy B, Darlington RB. 2010 Late still equals large. *Brain Behav. Evol*. **75**, 4–6. (doi:10.1159/000295350)
79. Herculano-Houzel S. 2011 Not all brains are made the same: new views on brain scaling in evolution. *Brain Behav. Evol*. **78**, 22–36. (doi:10.1159/000327318)
80. Herculano-Houzel S, Manger PR, Kaas JH. 2014 Brain scaling in mammalian evolution as a consequence of concerted and mosaic changes in numbers of neurons and average neuronal cell size. *Front. Neuroanat*. **8**, 77.
81. Barton RA. 2012 Embodied cognitive evolution and the cerebellum. *Phil. Trans. R. Soc. B* **367**, 2097–2107. (doi:10.1098/rstb.2012.0112)
82. Gabi M, Neves K, Masseron C, Ribeiro PFM, Ventura-Antunes L, Torres L, Mota B, Kaas JH, Herculano-Houzel S. 2016 No relative expansion of the number of prefrontal neurons in primate and human evolution. *Proc. Natl Acad. Sci. USA* **113** 9617–9622. (doi:10.1073/pnas.1610178113)
83. Charvet CJ, Cahalane DJ, Finlay BL. 2015 Systematic, cross-cortex variation in neuron numbers in rodents and primates. *Cereb. Cortex*. **25**, 147–160. (doi:10.1093/cercor/bht214)
84. Anderson ML, Finlay BL. 2013 Allocating structure to function: the strong links between neuroplasticity and natural selection. *Front. Hum. Neurosci*. **7**, 918.
85. Willemet R. 2012 Understanding the evolution of mammalian brain structures; the need for a (new) cerebro type approach. *Brain Sci*. **2**, 203–224. (doi:10.3390/brainsci2020203)
86. Charvet CJ, Finlay BL. 2012 Embracing covariation in brain evolution: large brains, extended development, and flexible primate social systems. *Prog. Brain Res*. **195**, 71–87. (doi:10.1016/B978-0-444-53860-4.00004-0)
87. Weisbecker V. 2009 Why 'late equals large' does not work. *Neuroscience* **164**, 1648–1652. (doi:10.1016/j.neuroscience.2009.09.027)
88. Menuet A, Alunni A, Joly J-S, Jeffery WR, Rétaux S. 2007 Expanded expression of Sonic Hedgehog in *Astyanax* cavefish: multiple consequences on forebrain development and evolution. *Development* **134**, 845–855. (doi:10.1242/dev.02780)
89. Sylvester JB, Rich CA, Loh Y-HE, van Staaden MJ, Fraser GJ, Streelman JT. 2010 Brain diversity evolves via differences in patterning. *Proc. Natl. Acad. Sci. USA* **107**, 9718–9723. (doi:10.1073/pnas.1000395107)
90. Charvet CJ, Striedter GF. 2009 Developmental origins of mosaic brain evolution: morphometric analysis of the developing zebra finch brain. *J. Comp. Neurol*. **514**, 203–213. (doi:10.1002/cne.22005)
91. Striedter GF, Charvet CJ. 2008 Developmental origins of species differences in telencephalon and tectum size: morphometric comparisons between a parakeet (*Melopsittacus undulatus*) and a quail (*Colinus virgianus*). *J. Comp. Neurol*. **507**, 1663–1675. (doi:10.1002/cne.21640)
92. Striedter GF, Charvet CJ. 2009 Telencephalon enlargement by the convergent evolution of expanded subventricular zones. *Biol. Lett*. **5**, 134–137. (doi:10.1098/rsbl.2008.0439)
93. Dyer MA, Martins R, Filho S, Muniz APC, Carlos L, Silveira L, Cepko CL, Finlay BL. 2009 Developmental sources of conservation and variation in the evolution of the primate eye. *Proc. Natl Acad. Sci. USA* 2015 **106**, 8963–8968. (doi:10.1073/pnas.0901484106)
94. Lewitus E, Kelava I, Kalinka AT, Tomancak P, Huttner WB. 2013 An adaptive threshold in mammalian neocortical evolution. *PLoS Biol*. **12**, 38.
95. Charvet CJ, Striedter GF. 2009 Developmental basis for telencephalon expansion in waterfowl: enlargement prior to neurogenesis. *Proc. R. Soc. B* **276**, 3421–3427. (doi:10.1098/rspb.2009.0888)
96. Buzi G, Lander AD, Khammash M. 2015 Cell lineage branching as a strategy for proliferative control. *BMC Biol*. **13**, 13. (doi:10.1186/s12915-015-0122-8)
97. Götz M, Huttner WB. 2005 The cell biology of neurogenesis. *Nat. Rev. Mol. Cell Biol*. **6**, 777–788. (doi:10.1038/nrm1739)
98. Kitisin K *et al.* 2007 Disruption of transforming growth factor-beta signaling through beta-spectrin ELF leads to hepatocellular cancer through cyclin D1 activation. *Oncogene* **26**, 7103–7110. (doi:10.1038/sj.onc.1210513)
99. Gámez B, Rodriguez-Carballo E, Ventura F. 2013 BMP signaling in telencephalic neural cell specification and maturation. *Front. Cell Neurosci*. **7**, 87. (doi:10.3389/fncel.2013.00087)
100. Kornack DR, Rakic P. 1998 Changes in cell-cycle kinetics during the development and evolution of primate neocortex. *Proc. Natl Acad. Sci. USA* **95**, 1242–1246. (doi:10.1073/pnas.95.3.1242)
101. Charvet CJ, Striedter GF. 2010 Bigger brains cycle faster before neurogenesis begins: a comparison of brain development between chickens and bobwhite quail. *Proc. Biol. Sci*. **277**, 3469–3475. (doi:10.1098/rspb.2010.0811)
102. Dehay C, Kennedy H. 2007 Cell-cycle control and cortical development. *Nat. Rev. Neurosci*. **8**, 438–450. (doi:10.1038/nrn2097)
103. Workman AD, Charvet CJ, Clancy B, Darlington RB, Finlay BL. 2013 Modeling transformations of neurodevelopmental sequences across mammalian species. *J. Neurosci*. **33**, 7368–7383. (doi:10.1523/JNEUROSCI.5746-12.2013)
104. Charvet CJ, Striedter GF, Finlay BL. 2011 Evo-devo and brain scaling: candidate developmental mechanisms for variation and constancy in vertebrate brain evolution. *Brain Behav. Evol*. **78**, 248–257. (doi:10.1159/000329851)
105. Sylvester JB, Pottin K, Streelman JT. 2011 Integrated brain diversification along the early neuraxes. *Brain Behav. Evol*. **78**, 237–247. (doi:10.1159/000329840)
106. Mars RB, Neubert F-X, Verhagen L, Sallet J, Miller KL, Dunbar RIM, Barton RA. 2014 Primate comparative neuroscience using magnetic resonance imaging: promises and challenges. *Front. Neurosci*. **8**, 1–11. (doi:10.3389/fnins.2014.00298)
107. Baker J, Meade A, Pagel M, Venditti C. 2016 Positive phenotypic selection inferred from phylogenies. *Biol. J. Linn. Soc*. **118**, 95–115. (doi:10.1111/bij.12649)